Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte H. MICHAEL SHEPARD and JAMES E. TALMADGE

Appeal No. 1999-1433
Application No. 08/453,852

ON BRIEF

Before ELLIS, SCHEINER and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 37 C.F.R. § 134 from the examiner's final rejection of claims 1-7, 11 and 14, all the claims remaining in the application. Claims 8-10, 12, 13 and 15-21 have been canceled.

Claims 1, 3, 5 and 11 are illustrative of the subject matter on appeal and read as follows:

1. A method for enhancing a humoral or cellular immune response in an animal comprising administering to the animal

(a) a non-tumor substance against which it is desired to raise the immune response; and

(b) an adjuvant effective amount of tumor necrosis factor-alpha.

3. The method of claim 2 wherein the substance is administered in the form of a conjugate with a microbial or viral polypeptide.

5. The method of claim 1 wherein the substance is native to the animal.

11. The method of claim 1 wherein the substance is an animal virus antigen.

The references relied upon by the examiner are:

Cohen et al. (Cohen)	4,709,011	Nov. 24, 1987
Riggs	4,812,554	Mar. 14, 1989
Shepard et al. (Shepard)	4,963,354	Oct. 16, 1990

Staruch et al. (Staruch), "The Adjuvanticity of Interleukin 1 In Vivo," J. Immunology, Vol. 130, pp. 2191-2194 (1983).

Beutler et al. (Beutler), "Passive Immunization Against Cachectin/Tumor Necrosis Factor Protects Mice from Lethal Effect of Endotoxin," Science, Vol. 229, pp. 869-871 (1985).

Kato et al. (Kato), "Comparative Studies on Adjuvanticity of Klebsiella O3 Lipopolysaccharide and Its Lipid A and Polysaccharide Fractions," Immunology, Vol. 54, pp. 317-324 (1985).

Bachwich et al. (Bachwich), "Tumor Necrosis Factor Stimulates Interleukin-1 and Prostaglandin E_2 Production In Resting Macrophages," Biochemical and Biophysical Research Communications, Vol. 136, pp. 94-101 (1986).

Kornbluth et al. (Kornbluth), "Tumor Necrosis Factor Production by Human Monocytes is a Regulated event: Induction of TNF-α-Mediated Cellular Cytotoxicity by Endotoxin", J. Immunology, Vol. 137, pp. 2585-2591 (1986).

The claims stand rejected as follows:

I. Claims 1, 2, 4, 5 and 14 stand rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 and 8 of U.S. Patent No. 4,963,354.

II. Claims 5 and 6 stand rejected under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Answer, pp. 4-5.

III. Claims 1 and 5 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure.

IV. Claims 1, 2, 4, and 14 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kato and Beutler or Kornbluth.

V. Claims 1, 2, 4, and 14 stand rejected under 35 U.S.C. § 103 as being unpatentable over Staruch and Bachwich.

VI. Claims 3, 6 and 7 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kato and Beutler or Kornbluth, in further view of Riggs.

VII. Claims 3, 6 and 7 stand rejected under 35 U.S.C. § 103 as being unpatentable over Staruch, Bachwich and Riggs.

VIII. Claim 11 stands rejected under 35 U.S.C. § 103 as being unpatentable over Kato and Beutler or Kornbluth, in further view of Cohen.

IX. Claim 11 stands rejected under 35 U.S.C. § 103 as being unpatentable over Staruch, Bachwich and Cohen.

We affirm Rejection I and reverse Rejections II-IX.

Background

Tumor necrosis factors (TNF-α and TNF-β) are cytokines[1] which are produced by monocytes and lymphocytes. Specification, p. 4. According to the specification, prior to the present invention, TNF-α and TNF-β had been shown to kill neoplastic tissue selectively, in vitro and in vivo, but their true in vivo function was still unclear. Id. Biologic studies were said to strongly suggest that TNFs played an important role in the immunomodulatory and inflammatory responses. Id.

As indicated by the claims, the present invention is directed to a method of enhancing an immune response in an animal to a non-tumor substance by administering said substance and an adjuvant-effective amount of TNF-α.

[1] Cytokines are hormone-like peptides or glycopeptides which act as a signal or mediator between cells.

Discussion

I. The double patenting rejection

The examiner has rejected claims 1, 2, 4, 5 and 14 under the judicially-created doctrine of obviousness-type double patenting. The examiner argues that the present claims, which are directed to enhancing an immune response to any non-tumor antigen using tumor necrosis factor (TNF), would have been obvious to one of ordinary skill in the art in view of claims 1-5 and 8 of U.S. Patent 4,963,354 which describe a method of enhancing an immune response to a tumor antigen using TNF. Answer, p. 4.

In response, the appellants do not contest the examiner's rejection. Rather, they simply state that they will file a terminal disclaimer once there is an indication of allowable subject matter. Brief, p. 17. However, an intention to file a terminal disclaimer is not sufficient to overcome the rejection. Accordingly, Rejection I is affirmed.

II. The 35 U.S.C. § 112, first paragraph, rejections

A. Written description/new matter

The examiner argues that the subject matter of claims 5 and 6 is not supported by the specification as originally filed. According to the examiner, there is no basis for a "native" substance in the specification and, therefore, the use of this term in claim 5 constitutes the introduction of new matter. Answer, p. 5. We disagree.

We point out that it is not necessary for the specification to describe the claimed

invention ipsissimis verbis; all that is required is that it reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. Union Oil of California v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1119 (Fed. Cir. 1992); In re Gosteli, 872 F.2d 1008,1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978).

Here, we agree with the appellants that the teachings of the specification as a whole, reasonably convey to those skilled in the art that substances against which it may be desired to induce an immune response, can include those substances which are "native" to the host animal. See, e.g., the specification, p. 3, lines 14-25; p. 11, lines 9-13. We find the term "native" in claim 5 to have the same meaning as the terms "endogenous" and "homologous" in the specification. That is, we find, and the examiner appears to agree,[2] that all of these terms are synonymous in that they all refer to something which is not foreign to the animal host.

Accordingly, Rejection II is reversed.

B. Enablement

[2] We direct attention to the enablement rejection wherein the examiner states that the method of claim 5 involves the use of "a substance native to the animal, rather than foreign to the animal." Answer, p. 5. Thus, it is not clear to us as to why the examiner has even raised this issue under the second paragraph of § 112.

In view of its brevity, we reproduce the examiner's enablement rejection in its entirety. The examiner argues:

> Claim 5 is directed to a method of enhancing an immune response to a substance native to the animal, rather than foreign to the animal. While auto-immune diseases are known, it is not art-recognized that animals can be administered a native substance that their immune system should recognize as "self" and have an immune response. The specification does not teach how to accomplish this method that is not art recognized. Therefore, this method is not enabled [Answer, p. 5].

We find the examiner's position untenable.

The first paragraph of § 112 requires, inter alia, that the specification enable those skilled in the art to which it pertains to make and use the claimed invention. PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); In re Wright, 999 F.2d 1557, 1561, 27 USPQ 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1448, 1444 (Fed. Cir. 1991). Although the statute does not so state, our appellate reviewing court has held that enablement requires that the specification teach such persons to make and use the claimed invention without "undue experimentation." In re Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444. The court also set forth the factors to be considered in determining whether a disclosure would require undue experimentation. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Those factors include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Here, we find that the examiner has not provided any explanation as to why it would have required undue experimentation for one skilled in the art to make and use the claimed invention. Nor does the examiner make any mention of the Wands factors. Rather, we find that the examiner's rejection consists only of an unsupported assertion that the technique of inducing an immune response by administering a native substance is not art-recognized. Answer, p. 5.

Accordingly, we reverse Rejection III.

III. The § 103 rejections

A. The rejection of claims 1, 2, 4 and 14 over Kato and Beutler or Kornbluth.

The examiner has premised her conclusion of obviousness on the teachings of either Kato and Beutler, or Kato and Kornbluth. To that end we find:

1. Kato discloses that lipopolysaccharide (LPS) derived from Klebsiella O3 is a strong adjuvant. Kato, p. 31, col. 1, lines 1-6. Kato .....

2. Beutler discloses that mice which are passively immunized with anti-TNF antibody are protected against the lethal effect of the LPS endotoxin produced by Escherichia coli. Beutler, p. 869, the abstract. Beutler reports that

> These data give evidence for the role of cachectin/TNF in mediating the lethal effects of LPS. Cachectin/TNF is clearly only one of the mediators responsible for the numerous pathological effects evoked by LPS, since the passively immunized mice become febrile, and continue to appear ill and distressed. It is possible, for example that cachectin/TNF acts in concert with other mediators (for example, interleukin-1, interferons, and lymphotoxin) in order to elicit the lethal effect of LPS).
>
> ***

> ... In LPS-sensitive species, TNF may play a more prominent role as a mediator of shock. Immunization against TNF might then be expected to yield a higher level of protection. Beutler, p. 871, paras. 2-3.

3. Kornbluth discloses the use of a monoclonal antibody specific for TNF-α to neutralize the effects of LPS on actinomycin D-treated WEHI 164 cells (a murine fibrosarcoma line), in vitro.

The examiner contends that the teachings of the references "render it obvious that the adjuvant and toxic effects of the exogenous LPS are mediated through the endogenous release of TNF because Kato et al. teach that LPS is an adjuvant and Beutler et al. or Kornbluth et al. teach that the effects of exogenously administered LPS is mediated through TNF." Answer, p. 6. According to the examiner, the use of TNF as an adjuvant would have been obvious to those of ordinary skill in the art because Beutler taught that LPS was an adjuvant and "one would reasonably expect that the mediator of LPS activity would also be an adjuvant." Id.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available in the art would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). In this

case, the examiner must establish that one of ordinary skill in the art would have understood from the teachings of the applied prior art that (i) TNF-α is an adjuvant, and (ii) TNF-α exerts its adjuvant effect in an antigen-specific manner. This the examiner has not done.

Here, we find the examiner's diagram with respect to the black box to be disingenuous. Answer, p. 6. As we understand it, the examiner's model is based on the teachings of Beutler or Kornbluth and depicts the administration of LPS (a non-tumor substance) in an animal which results in an interaction with TNF. However, because the references do not disclose the nature of the LPS-TNF interaction, the examiner has inserted a block box, out of which pops the appellants' invention. The problem is that we do not find, and the examiner has not pointed out, any teachings or suggestions in Beutler or Kornbluth that TNF acts as an adjuvant to enhance the toxic effects of LPS. On this record, we only find the suggestion to use TNF as an adjuvant in the appellants' disclosure. Thus, we agree with the appellants that the examiner has engaged in impermissible hindsight in making her determination of obviousness. In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991)("It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps"); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)("To imbue

one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

Accordingly, we reverse Rejection IV.

B. The rejection of claims 1, 2, 4 and 14 over Staruch and Bachwich.

The examiner urges that claims 1, 2, 4 and 14 would have been obvious in view of the teachings of Staruch and Bachwich.

Staruch discloses that interleukin 1 (IL-1), a protein produced by macrophages which was known to modulate many of a host's defensive responses to infection, may also mediate the effects of some adjuvants. Staruch, p. 2191, the abstract and col. 1, para. 3. Staruch reports that when IL-1 is administered with bovine serum albumin (BSA) that it acts as an adjuvant to enhance the antibody response of mice to BSA. Id., p. 2193, e.g., Table V. Staruch states that the observed enhancement of antibody responses using IL-1 is consistent with "the hypothesis that many agents exert their adjuvant effects by inducing the release of IL 1 from macrophages." Id., p. 2193, col. 2, second complete para.

Bachwich discloses that the administration of TNF stimulates the production of IL-1 and prostaglandin E_2 (PGE) from murine macrophages, in vitro. Bachwich, p. 94,

the abstract. Bachwich further discloses that TNF and LPS act in an additive manner to stimulate macrophages to produce more IL-1 than either substance alone. Id., p. 100, lines 11-12.

The examiner argues that it would have been obvious to one of ordinary skill in the art to "administer TNF to cause the release of IL-1 to elicit an immune adjuvant response in mice against an antigen" because Staruch discloses that the adjuvant effects of LPS are mediated through IL-1 and Bachwich discloses that TNF (and LPS) stimulate the release of IL-1. Answer, p. 7. We disagree.

As we discussed above, in this case the burden is on the examiner to establish that the applied prior art teaches or suggests that (i) TNF-α is an adjuvant, and (ii) TNF-α exerts its adjuvant effect in an antigen-specific manner.

To that end, we find that (i) Staruch discloses that when IL-1 is administered to an animal host in conjunction with BSA, IL-1 acts as an adjuvant to enhance the antibody response to BSA, and (ii) Bachwich discloses that TNF stimulates IL-1 (and PGE_2) production by macrophages, in vitro. However, Bachwich does not characterize the TNF-induced IL-1 release. Thus, what is missing from the applied prior art is a teaching or suggestion that when TNF is administered to an animal host in conjunction with an antigen, that TNF will act as an adjuvant and stimulate an enhanced immune response to said antigen. Again, we find that the examiner has tried to compensate for this deficiency in the teachings of references by shoving those components which are taught therein and which are required to arrive at the claimed method into a black box. Answer,

p. 7. As indicated above, we find the black box model to be inappropriate. On this record, the only place where we find a suggestion (i) that TNF is an adjuvant, and (ii) to administer TNF in combination with a non-tumor substance in an animal in order to stimulate a humoral or cellular immune response to said substance, is in the appellant's specification. Accordingly, we again agree with the appellants that the examiner has relied on impermissible hindsight in arriving at her conclusion of obviousness. In re Gorman, 933 F.2d at 987, 18 USPQ2d at 1888; Interconnect Planning Corp. v. Feil, 774 F.2d at 1138, 227 USPQ at 547; W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d at 1553, 220 USPQ at 312-313.

Therefore, Rejection V is reversed.

C. The rejections of claims 3, 6, 7 and 11 in further view of Riggs and Cohen.

The examiner urges that claims 3, 6, 7 and 11 would have been further obvious in view of the teachings of Riggs and Cohen. Answer, pp. 8-10.

With respect to the prior art we point out that the examiner merely states that the "teachings of Riggs et al. are discussed above." Answer, p. 8. We have carefully reviewed the Examiner's Answer, but we find no discussion of the Riggs patent. As to Cohen, we find that the patent discloses the preparation of vaccine compositions comprising the Herpes simplex virus (HSV) envelope glycoprotein, gD. Cohen, the abstract; col. 1, lines 17-25; col. 6, line 27- col. 7, line 24. Cohen further discloses that the vaccine compositions can include an adjuvant such as "Freund's Complete Adjuvant,

saponin, alum and the like." Id., col. 7, lines 20-24.

Here, we direct attention to our discussions above wherein we hold that the examiner has not met her burden of establishing that the inventions described in claims 1, 2, 4 and 14 would have been obvious in view of the teachings of Kato, Beutler, Staruch and Bachwich. Thus, we agree with the appellants that the teachings of Riggs and Cohen do not rectify the deficiencies of the primary references.

Accordingly, Rejections VI-IX are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

JOAN ELLIS Administrative Patent Judge	)
TONI R. SCHEINER Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES
LORA GREEN Administrative Patent Judge	)

Genentech, Inc.
Diane L. Marschang

460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990

JE/ki